REMARKS

Claims 31-52 are pending in the application. Claims 36, 47, and 48 have been amended herein to remove specific phrases as described below.

Claims 53-64 have been added herein. Support for these claims can be found in the specification at, *inter alia*, page 16, line 8 to page 17, line 24.

Accordingly, no new matter has been introduced by these amendments and new claims.

Therefore, after entry of this amendment, claims 31-64 will be pending in this application.

The outstanding rejections are addressed individually below.

I. Claims 31-52 are enabled by the specification as filed.

The outstanding Office Action states that claims 31-52 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. In particular, some specific alleged issues that the Office Action describes include that the specification fails to disclose the culturing conditions in which the fibroblast cells when cultured produce type I and type III collagens and tenascin. In addition, the Office Action states that the specification fails to identify type I and type III collagens and tenascin in the extracellular matrix secreted by cultured fibroblasts. The Office Action further states that the specification fails to disclose that fibroblast cells derived from specific tissues are capable of synthesizing extracellular components under any and all culture conditions. Furthermore, the Office Action states that the specification fails to disclose that use of any and all culture conditions would lead to the formation of an epidermal layer in a cultured skin construct. (Office Action, page 4.) Applicants respectfully traverse this rejection. Applicants respectfully submit that these claims are enabled by the specification as filed.

M.P.E.P § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled

in the art can make and use the invention without undue experimentation." The same section further states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

The specification does teach one of skill in the art how to *make* the invention. *See, e.g.*, the specification at page 7, lines 4-19 (disclosing various sources of fibroblast cell strains), at page 9, line 1 to page 10, line 20 (teaching suitable vessels and growth surfaces for the culture of fibroblast cells), at page 11, line 11 to page 17, line 24 (teaching culture media formulations for culturing the fibroblasts), at page 17, lines 25-28 (describing environmental conditions for culturing the fibroblasts), at page 17, line 29 through page 18, line 26 (teaching seeding and culturing the fibroblasts in order to obtain a layer of cultured fibroblasts and extracellular matrix), and at page 19, line 7 to page 20, line 11 (teaching application of an epithelial cell layer to the construct).

Additionally, the specification does teach one of skill in the art how to *use* the invention. *See, e.g.*, the specification at page 24, line 7 to page 25, line 4 (teaching methods for grafting the skin construct of the invention to a patient).

Therefore, the specification has fully enabled the invention as claimed because it teaches how to <u>make and use</u> the invention without undue experimentation.

With regard to the production of types I and III collagen and tenascin, the specification states at page 4, lines 12-13 that "[d]elayed reduction SDS-PAGE has detected the presence of both type I and type III collagen in these constructs . . . ." The specification of the instant application clearly states that, "[t]he predominant major extracellular matrix component produced by fibroblasts is fibrillar collagen, particularly collagen type I" and continues to state that

> other collagens, both fibrillar and non-fibrillar collagen from the collagen family such as collagen types II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, may be produced by use of the appropriate cell type. Similarly, other matrix proteins which can be produced and deposited using the current method include, but are not limited to elastin; proteoglycans such as decorin or biglycan;

> or glycoproteins such as tenascin; vitronectin; fibronectin; laminin, thrombospondin I, and glycosaminoglycans (GAG) such as hyaluronic acid (HA).

Page 8, lines 20-29.

Furthermore, the specification states at page 4, lines 17-18 that the "produced tissue also stains positive for tenascin, an extracellular matrix glycoprotein found, for example, in mesenchyme or tissues under repair."

With regard to the fact that the specification allegedly does not enable the claims under any and all culture conditions, Applicants respectfully submit that the specification explicitly provides numerous examples of culture conditions under which the claimed cultured tissue constructs can be produced and for use in the claimed methods for producing the cultured tissue constructs. For instance: general culture conditions and chemically defined media are described at page 11, line 11 to page 12, line 12; culture medium and various additives thereto are described at page 12, line 13 to page 15, line 4; preparation of medium is described at page 15, line 5 to page 16, line 2; matrix production medium and its preparation are described at page 16, line 3 to page 17, line 24; and culturing environmental conditions are described at page 17, lines 25-28.

Furthermore, the working Examples provide detailed descriptions of various media used, including, by way of nonlimiting example, growth medium (*see, e.g.*, Example 1, page 25, lines 13-16; Example 6, page 33, line 28 to page 34, line 2; Example 10, page 37, lines 23-26; Example 11, page 38, lines 23-26; and Example 12, page 40, lines 22-25); production medium (*see, e.g.*, Example 1, page 26, lines 3-14; Example 9, page 37, lines 1-11; Example 10, page 37, line 30 to page 38, line 10; and Example 11, page 39, line 21 to page 40, line 1); epidermalization medium (*see, e.g.*, Example 2, page 28, lines 10-22; Example 4, page 32, lines 4-15; and Example 16, page 46, line 22 to page 47, line 3); cornification medium (*see, e.g.*, Example 2, page 29, lines 9-21); maintenance medium (*see, e.g.*, Example 2, page 29, line 22 to page 30, line 3); chemically defined medium (*see, e.g.*, Example 3, page 30, line 23 to page 31, line 3; and Example 15, page 44, line 29 to

page 45, line 6); seed medium (*see, e.g.*, Example 9, page 36, lines 22-30; and Example 11, page 39, lines 10-19); and other Examples which refer back to media previously described.

Further, Applicants have shown, in several of the Examples, a first layer of cultured fibroblast cells that produce an extracellular matrix layer. Example 1 describes the formation of a collagenous matrix formed by human neonatal foreskin fibroblasts. Example 3 describes the *in vitro* formation of a collagenous matrix by human neonatal foreskin fibroblasts in chemically defined medium. Example 5 describes the *in vitro* formation of a collagenous matrix by human Achilles tendon fibroblasts. Example 6 describes the *in vitro* formation of a collagenous matrix by transfected human neonatal foreskin fibroblasts. Example 9 describes the *in vitro* formation of a matrix by human corneal keratocytes. Example 10 describes the *in vitro* formation of a collagenous matrix by human neonatal foreskin fibroblasts seeded in production media. Example 11 describes the *in vitro* formation of a collagenous matrix by pig dermal fibroblasts. Example 15 describes the *in vitro* formation of three collagenous matrices by human neonatal foreskin fibroblasts in three differently supplemented chemically defined media. Example 17 describes the formation of a collagenous matrix by human buccal fibroblasts. The extracellular matrix layer has measurable physical and mechanical properties as shown in Example 14 where the cell-matrix constructs produced in Examples 1 (cell-matrix construct), 2 (cell-matrix construct with a keratinocyte layer thereon) and 3 (cell-matrix construct formed in defined medium) are evaluated.

Accordingly, Applicants respectfully submit that claims 31-52 are enabled by the specification as filed. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

II. Claims 31-32, 36-38, and 48-49 are not anticipated under 35 U.S.C. § 102(b).

Claims 31-32, 36-38, and 48-49 stand rejected as allegedly being anticipated by Fleishmajer *et al.* under 35 U.S.C. § 102(b). Applicants respectfully traverse this rejection.

M.P.E.P. 2131 provides that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). . . . "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim . . . .

Although Applicants do not necessarily agree with the characterization of the reference, Applicants aver that Fleishmajer *et al.* does not disclose a cultured skin or tissue construct wherein the "extracellular matrix is produced by the cultured [dermal] fibroblast cells in the absence of exogenous matrix components." In contrast, Fleishmajer *et al.* disclose that the fibroblasts were seeded onto nylon mesh. (Page 1359, second column.) This teaching is also acknowledged in the Office Action at page 6. Thus, because of this distinction regarding how the fibroblasts are cultured, the § 102(b) rejection is unsupported by the art. Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Claims 33-35, 39-47, and 50-52 are not obvious under 35 U.S.C. § 103(a).

Claims 33-35, 39-47, and 50-52 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Fleishmajer *et al.* in view of Naughton *et al.* (U.S. Patent No. 5,266,480). Applicants respectfully traverse this rejection.

M.P.E.P. § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art, and not based on applicant's disclosure.

Although Applicants do not necessarily agree with the characterization of Fleishmajer *et al.* and Naughton *et al.*, Applicants aver that, as discussed above, Fleishmajer *et al.* does not disclose a cultured skin or tissue construct wherein the "extracellular matrix is produced by the cultured [dermal] fibroblast cells in the absence of exogenous matrix components." Furthermore, Naughton *et al.* also does not disclose this claim language. Moreover, Naughton *et al.* teaches away from Applicants' claimed invention through its disclosure of the use of exogenous matrix components, *see, e.g.*, the definition of "three-dimensional matrix" at Col. 6, lines 22-27 and the materials that can be used to form the matrix at Col. 10, line 65 to Col. 11, line 30.

Accordingly, Applicants respectfully submit that the cited references do not teach or suggest all of the claim limitations; therefore, there is no *prima facie* case for obviousness based on these references. Applicants respectfully request that this rejection be reconsidered and withdrawn.

IV. Claims 32, 36, 43, and 47-48 are not indefinite under 35 U.S.C. § 112, second paragraph.

Claims 32, 36, 43, and 47- 48 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

Claims 32 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, because it is purportedly unclear what encompasses a "chemically defined media." Applicants respectfully submit that this term is definite in light of the description in the specification. Chemically defined media is described in the specification at, *inter alia*, page 11, line 17 to page 12, line 12. Furthermore, such media is described in the working Examples at, *inter alia*, Example 3, page 30, line 23 to page 31, line 3, and Example 15, page 44, line 29 to page 45, line 6. As described in the specification, "chemically defined culture media" is "media free of undefined animal organ or tissue extracts, for example, serum, pituitary extract, hypothalamic extract, placental extract,

or embryonic extract or proteins and factors secreted by feeder cells." (*See* Specification at page 11, lines 25-27.) Applicants respectfully submit that this term is definite when interpreted in light of the specification. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 36 and 47 stand rejected under 35 U.S.C. § 112, second paragraph, because it is allegedly unclear what are "tissue-like handling" properties. Applicants respectfully disagree with this rejection; however, in order to expedite prosecution this claim language has been deleted from the claims. These amendments are not considered to be narrowing amendments. Applicants respectfully submit that this rejection is moot in light of these amendments.

Claim 48 stands rejected under 35 U.S.C. § 112, second paragraph, because it is allegedly unclear what comprises "second culture media" that stimulates fibroblast cells to synthesize the claimed extracellular matrix components. Applicants respectfully disagree with this rejection; however, in order to expedite prosecution, claim 48 has been amended to delete the phrase "in a second culture medium." This amendment is not considered to be a narrowing amendment. Applicants respectfully submit that this rejection is moot in light of this amendment.

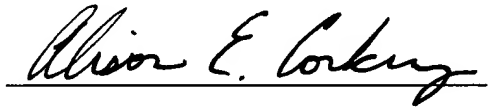
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the rejections contained in the Office Action mailed on March 10, 2004, have been overcome, and that the pending claims, claims 31-64, are in condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, she is invited to contact the undersigned at the telephone number provided below.

Applicants enclose herewith a petition for a one month extension of time pursuant to 37 C.F.R. § 1.136, up to and including July 12, 2004 (July 10, 2004 being a Saturday, and July 11, 2004 being a Sunday). Please charge Deposit Account No. 08-0219 the $55.00 fee (small entity) for this purpose.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,



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